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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,743	05/26/2005	Hiroyuki Osada	1261-0156PUS1	6909

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EXAMINER	
CHUNG, SUSANNAH LEE	

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
07/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/516,743	OSADA ET AL.	
	Examiner	Art Unit	
	SUSANNAH CHUNG	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *RCE filed 4/9/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,5-8 and 10-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *5,7 and 10-12* is/are allowed.

6)☒ Claim(s) *3,6,8 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 3, 5-8 and 10-13 are pending in the instant application. Claims 1-2, 4 and 9 are canceled.

RCE

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 4/9/2008 has been entered.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for the reasons describe below.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented [by the inventor];
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary [to make and/or use the invention].

The eight Wands factors are applied to Claim 13 of the present invention below:

(1) The Nature of the Invention

Claim 13 is directed to

13. (**Previously Presented**) A method for inhibiting growth of neuroblastoma comprising administering an effective amount of the pharmaceutical composition of claim 8 to a patient in need thereof.

(2) The Breadth of the claims

Claim 13 will be give its broadest reasonable interpretation. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, Claim 13 which is directed to neuroblastoma in general will be

interpreted to encompass all forms of neuroblastoma, regardless of whether it is a primary or secondary method of use.

(3) The state of the prior art

The state of the pharmaceutical art in general involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat or prevent diseases such as neuroblastoma or cancer).

The state of the art at the time of this application is that the etiology and treatment of neuroblastomas is not well understood. Cancer therapy is challenging and highly unpredictable. Adding to the challenge are the many different cancer lines that all have different mechanisms of action and no two types of cancer could be said to share the same method of treatment. Currently, the most successful therapeutic treatments of low-risk neuroblastoma have focused on chemotherapy and stem cell research. The use of small molecules such as the instant compound of formula (I) or (III) to treat neuroblastoma is highly unpredictable.

The instant compound of formula (I) and (III) is Epolactaene, a natural product isolated from fungal strain Penicillium, which has been shown to possess neurite outgrowth activity in human neuroblastoma cell line SH-SY5Y (See Kuramochi et al., Tet. Lett., Vol. 40, 1999, 7371-7374, especially page 7371.) However, the specific mechanism by which epolactaene affects the cell line is unknown and was not disclosed in the literature. The state of the art appears to be that more research needs to be conducted. *Id.* at 7374.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

It is noted that the pharmaceutical art generally is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with the degree of unpredictability in the factors involved. In re Fisher, 427 F.2d 833, 839. Therefore, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute. Added to the unpredictability of the art itself is the question whether a showing of some activity in a very specific cell line could reliably and predictably applied to the treatment of all types of neuroblastoma. There is no absolute predictability, even in view of the high level of skill in the art.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses that the instantly claimed compounds showed activity in SH-SY5Y cells of human neuroblastomas in vitro. (See specification page 39).

(7) The presence or absence of working examples

The specification shows the activity of the instantly claimed compound in one cell line, SH-SY5Y human neuroblastoma. There is no IC50 data or population data or other data to support the use of the instantly claimed compound in the treatment of neuroblastoma.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for the role of the instantly claimed compounds in the treatment of neuroblastoma, it would cause a skilled artisan an undue amount of experimentation to practice this invention to determine which

patients with which diseases would benefit from which of the many claimed compounds within the scope of the invention with a reasonable expectation of success.

The instant breadth of the claim(s) is broader than the disclosure, specifically, the instant claim is directed to the treatment of neuroblastoma in general, but the specification, prior art or instant disclosure does not provide support for this.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the variable Y is indefinite. The definition "a protecting group of a hydroxyl group" is overly broad and the metes and bounds of the claim cannot be ascertained. Therefore, the claim is indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

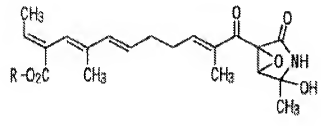
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

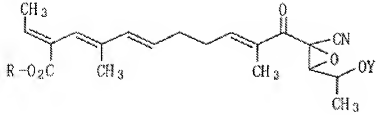
Claims 3, 6 and 8 are rejected under 35 U.S.C. 103(a) as being anticipated by Hayashi et al., Chem. Lett., Vol. 27(4), 1998, p. 313-314, especially page 313 and Kuramochi et al., Tet. Lett., Vol. 40, 1999, 7371-7374, especially page 7371.

Applicants claims relate to compound of Formula (I),



, in claim 3, wherein R is tert-butyl, wherein the compound is used to treat neuroblastoma cell line SH-SY5Y.

Applicants claims relate to compound of Formula (III),



, in claim 6, wherein R is alkyl or aryl and Y is a hydroxyl protecting group, wherein the compound is used to treat neuroblastoma cell line SH-SY5Y.

Determination of the scope and content of the prior art (MPEP § 2141.01)

Hayashi and Kuramochi teach the compound Epolactaene, which corresponds to Applicants instant formula (I), wherein R is methyl, and the process of making Epolactaene that render obvious the instantly claimed compound of formula (I) and (III). Hayashi and

Kuramochi also teaches that the instantly claimed compounds are active in neuroblastoma cell line SH-SY5Y.

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The difference between the prior art of Hayashi and Kuramochi and the instant claims is that they are homologues or structural isomers of the prior art compounds.

The difference between the prior art of Hayashi and Kuramochi and instantly claimed formula (I) is that in the prior art R is alkyl, wherein the alkyl group is methyl, while in the instant application R is alkyl, wherein the alkyl group is tert-butyl.

The difference between the prior art of Hayashi and Kuramochi and instantly claimed formula (III) is that in the instant claimed formula contains a –CN moiety instead of an -NH2 moiety.

Finding of prima facie obviousness – rationale and motivation (MPEP § 2142-2413)

However, in the absence of showing unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention when faced with Hayashi and Kuramochi to make the instantly claimed derivatives of a known product. The instantly claimed compounds and prior art compounds are common derivatives, such as isomers, homologs, or bioisosteres of one another. Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See MPEP 2144.09(II).

Prior art structures do not have to be true homologs or isomers to render structurally similar compounds prima facie obvious. In re Payne, 606 F.2d 303, 203 USPQ 245 (CCPA 1979) (Claimed and prior art compounds were both directed to heterocyclic carbamoyloximino compounds having pesticidal activity. The only structural difference between the claimed and prior art compounds was that the ring structures of the claimed compounds had two carbon atoms between two sulfur atoms whereas the prior art ring structures had either one or three carbon atoms between two sulfur atoms. The court held that although the prior art compounds were not true homologs or isomers of the claimed compounds, the similarity between the chemical structures and properties is sufficiently close that one of ordinary skill in the art would have been motivated to make the claimed compounds in searching for new pesticides.). See MPEP 2144.09 (III).

Bioisosteres of compounds are well known in the art. See Patani et al., Chem Rev, 1996, Vol. 96 (8), especially page 3147. Patani teaches that there are traditional and nontraditional bioisosteres. For example, NH2 and CN are bioisosteres of one another. See Patani et al, at page 3154, Table 14.

The instant obviousness rejection is based on the close structural similarity of the instantly claimed compounds to the prior art compounds and the common utility shared among the compounds. There is an expectation among those of ordinary skill in the art that similar structural compounds will have similar properties and that modification of a known structure is mere experimentation within the means of a skilled artisan. See MPEP 2144.09(I). Therefore, claims 3, 6 and 8 are rejected as obvious over the prior art.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/REI-TSANG SHIAO /
Primary Examiner, Art Unit 1626

Susannah Chung, July 15, 2008